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Lipoproteína (a) e Risco Vascular

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DISSERTAÇÃO DE CANDIDATURA AO GRAU DE DOUTOR

APRESENTADA À FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

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Tudo,
menos deixar uma incerteza
no caminho.
Quem vier nesta mesma direção,
Veja as passadas dos meus pés,
E siga.
Saiba por elas que não foi traído,
Mesmo se me encontrar adormecido
De morte natural ou de fadiga.

Miguel Torga in Diário (I-VIII)

À Cinha
À Kelita, à Pepe e à Xia

À memória dos meus Pais

À minha Família
Aos meus Amigos

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Ao abrigo do Art.º 8 do Decreto-Lei 388/70,
fazem parte integrante desta dissertação as seguintes publicações:

LIPOPROTEIN(A) IN THE ROUTINE EVALUATION OF CARDIOVASCULAR RISK IN THE PORTUGUESE POPULATION

Joaquim A. Meireles-Brandão (M.D.)[1,2]; Lúcia R. Meireles-Brandão (M.D.)[2]; Rui Coelho (M.D., PhD.)[2];
Francisco Rocha-Gonçalves (M.D., PhD.)[1] (Publicado na Acta Médica Portuguesa)

LIPOPROTEIN(A) AS A KEY TARGET IN MULTIPLE THERAPEUTIC APPROCHES FOR CARDIOVASCULAR DISEASE

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A contribuição pessoal para a realização destes trabalhos consistiu na
conceção do projeto e submissão as estruturas regulatórias,
recolha de material, obtenção e análise dos dados e, redação dos manuscritos.

Lista de Abreviaturas

ACC Antagonistas dos Canais Cálcio
ACC/AHA *American College of Cardiology/American Heart Association*
ACEI *Angiotensin Converting Enzyme Inhibitor*
ADO Antidiabéticos Orais
ARA-II Antagonistas dos Recetores da Angiotensina II
ARB-II *Angiotensin II Receptor Blocker*
ASCVD *Atherosclerotic Cardiovascular Disease*
Apo(a) Apolipoproteina (a)
apoB Apolipoproteina B
BMI *Body Mass Index*
CCA *Calcium Channels Antagonists*
CRP Proteína-C Reativa
CV Cardiovascular
CVD *Cardiovascular Disease*
CVRF *Cardiovascular Risk Factors*
DCV Doença Cardiovascular
ECG *Eletrocardiograma*
FRS *Framingham Risk Score*
HDLc Colesterol das Lipoproteínas de Elevada Densidade
HgA1c Hemoglobina Glicada
IBP Inibidores da Bomba de Protões
IECA Inibidor Enzima Conversora da Angiotensina
IMC Índice de Massa Corporal
IMT *Intima Media Thickness*
INE Instituto Nacional de Estatística
LDLc Lipoproteína do Colesterol de Baixa Densidade
LEPT Proteína Transportadora de Esteres de Colesterol
Lp(a) Lipoproteína (a)
MAPA Monitorização Ambulatória da Pressão Arterial
mRNA micro RNA
NAFLD *Non Alcoholic Faty Liver Disease*
OAD *Oral Antidiabetic Drug*
PB Perímetro Braquial
PCT Prega Cutânea Tricipital
PCSK9 *Proprotein Convertase Subtilisin/Kexin Type 9*
SCORE *Systematic Coronary Risk Evaluation*
TSH Terapêutica Hormonal de Substituição
VLDLc Colesterol das Lipoproteínas de Muito Baixa Densidade

Índice

ABSTRACT

Lp(a) is a low-density lipoprotein (LDLc)-like particle that associates with major adverse cardiovascular events. It is consensual that Lp(a) elevation is an independent causal risk factor for CVD and that this risk becomes particularly high when patients simultaneously present high Lp(a) and LDLc values significantly increasing the incidence of CVD. However, the precise mechanism by which Lp(a) leads to CVD is still not defined, and can be explained by the fibrinolytic and pro-thrombotic properties. Or by virtue of its structural homology with Apo(a) with plasminogen as well as by the atherogenesis due cholesterol contained in Lp(a) and deposited in the intima. If this hypothesis is to be true, it will confirm that high concentra-tions of Lp(a) are associated with low risk of hemorrhages. Lp(a) acts as a lipoprotein carrier of oxidized phospholipids and, once in the sub endothelial space, it can be pro-inflammatory and probably retained. The oxidized phospholipids are prevalent in the vulnerable plaques and predictors of carotid and femoral atherosclerosis and are elevated in acute coronary syndromes.

Primary prevention may be the “touchstone”, certainly decisive to reduce the residual risk of CVD.

We conducted an observational, longitudinal retrospective study that took place between 1995 and 2015 conducted in a population of 516 patients with two or more personal and/or family cardiovascular risk factors (CVRF) and without CVD events.

After characterizing the sample, we proposed to evaluate the profile of Lp(a), to calculate the cardiovascular risk to 10 years using the most used scores: Framingham risk Score (FRS), Atherosclerotic cardiovascular disease (ASCVD) - ACC/AHA, Systematic coronary risk evaluation (Score)-ESC (high and low score). We verified a significant correlation between the values of Lp(a) and each of the scores of cardiovascular risk to 10 years.

A statistically significant correlation was also confirmed when we performed an identical exercise between Lp(a) in relation to the various traditional parameters and considered in the assessment of cardiovascular risk: clinical (IMT, BMI, Waist circumference, height) and laboratory (LDLc, HgA1c, CRP, homocysteine, VLDLc, fructosamine, total cholesterol, triglycerides, fibrinogen, uric acid). In relation to C-peptide, insulin did not find a significant relationship with the Lp(a) values, and it was noteworthy that the same was the case with the HDLc.

There is a significant relationship between the high values of Lp(a) and hepatic steatosis, and the Lp(a) values are elevated in patients with hepatic steatosis.

The patient’s lifestyle was also evaluated, considering the consumption of tobacco, ethylic habits, and regular aerobic physical activity. Regarding the evolution of these parameters between the beginning and the end of the study, it will be highlighted the great increase in the number of participants in aerobic physical activity, as well as the significant reduction in alcohol and tobacco consumption.

Considering the analysis of the pathologies observed they were distributed by their nosological groups of diseases: cerebrovascular, cardiovascular, metabolism and behavioral diseases. We proposed to verify the results of the treatments performed, considering for this purpose the therapeutics carried out grouped in the respective therapeutic groups.

Our results allow us to conclude the importance of the determination of Lp(a) as a biomarker of first-line vascular risk, and this was the first study that documented the significant correlation between elevated Lp(a) values and all markers of vascular risk, notably as well as non-alcoholic hepatic steatosis.

In view of the results obtained, we consider that Lp(a) should be integrated into routine biochemical evaluation, particularly in the screening of vascular risk, allowing an early diagnosis with consequent risk assessment. And because it is transversal to all therefore fundamental in primary prevention, allowing for a diagnosis, adequate and early interventions. This assumption does not apply to the other scores of calculation and stratification of cardiovascular risk to 10 years that to determine, include in its calculation the age (> 30 years), sex, smoking habits, blood pressure, lipids and several other CVRF (diabetes, hypertension, weight) by conditioning an early and adequate intervention in patients with high cardiovascular and metabolic risk despite age.

We can believe that phoenix was reborn from the ashes considering the results obtained and, taking into account the therapies performed during the study, we could therefore see that Lp(a) should constitute a therapeutic target as an indicator and protagonist of severity of vascular risk.

Henceforth and in primary prevention, all therapies aimed at the various CVRF should be considered and applied early in order to postpone the inexorable evolution of the atherosclerotic process. In the first therapeutic line and in order of importance, statins appear, followed by antiplatelet agents, allopurinol and antidepressant therapy. It should be considered whenever necessary and appropriate to the clinical situation, therapeutic with: calcium channels antagonists (CCA), angiotensin-converting enzyme inhibitors (ACEI), oral antidiabetics (OAD) and reuptake inhibitors of Angiotensin II (ARB-II). As a therapeutic adjuvant, adherence to healthy lifestyles is essential, thus contributing to a favorable prognosis regarding the containment and control of the atherosclerotic process.

RESUMO

A Lp(a) é uma lipoproteína de baixa densidade similar à LDLc, partícula que está associada à ocorrência de eventos cardiovasculares major. É consensual que a elevação de Lp(a) é um fator de risco independente causal para a DCV e, que este risco se torna particularmente elevado quando os doentes apresentam simultaneamente, valores de Lp(a) e de LDLc elevados aumentando de forma significativa a incidência da DCV. Contudo, ainda não está definido o mecanismo preciso pelo qual a Lp(a) conduz à DCV, podendo ser explicado pelas propriedades fibrinolíticas e pro trombóticas. Por força da sua homologia estrutural com a apo(a) com plasminogénio como também pela aterogénese devida ao colesterol contido na Lp(a) e depositado na íntima. Sendo que esta hipótese a ser verdadeira, confirmará que elevadas concentrações de Lp(a) estão associadas a baixo risco de hemorragias. A Lp(a) atua como um portador de lipoproteína dos fosfolípidos oxidados e, uma vez no espaço sub-endotelial pode ser pro-inflamatório e provavelmente retido. Os fosfolípidos oxidados são prevalentes nas placas vulneráveis e preditores de aterosclerose carotídea e femoral e, estão elevados nas síndromes coronárias agudas.

A prevenção primária poderá ser a "pedra de toque", certamente decisiva para reduzir o risco residual de DCV.

Realizamos um estudo observacional, longitudinal retrospectivo que decorreu entre 1995 e 2015 realizado numa população de 516 doentes portadores de dois ou mais fatores de risco cardiovascular (FRCV) pessoais e/ou familiares e sem eventos de DCV.

Após caracterização da amostra, propusemo-nos avaliar o seu perfil da Lp(a), calcular o risco cardiovascular a 10 anos utilizando as tabelas de algoritmos mais em uso: *Framingham Risk Score* (FRS), *Atherosclerotic Cardiovascular Disease* (ASCVD) - ACC/AHA, *Systematic Coronary Risk Evaluation* (SCORE) - ESC (*high and low score*). Verificamos uma correlação significativa entre os valores de Lp(a) e cada um dos scores do risco cardiovascular a 10 anos.

Uma correlação estatisticamente significativa ($p<0.001$) foi encontrada, quando efetuamos exercício idêntico entre a Lp(a) relativamente aos vários parâmetros tradicionais e considerados na avaliação do risco cardiovascular: clínicos (IMT, BMI, Circunferência abdominal, Estatura) e laboratoriais (LDLc, HgA1c, PCR, Homocisteína, VLDLc, Frutosamina, Colesterol total, Triglicerideos, Fibrinogénio, Ácido úrico). Relativamente ao Peptídeo C, Insulina não encontramos relação significativa com os valores de Lp(a), sendo de realçar que o mesmo sucedeu relativamente ao HDLc.

Há uma relação significativa ($p< 0.001$) entre os valores elevados de Lp(a) e a esteatose hepática sendo que os valores de Lp(a) estão elevados nos doentes com esteatose hepática.

Foi também avaliado o estilo de vida dos doentes, considerando-se para o efeito o consumo de tabaco, hábitos etílicos, actividade física regular aeróbica. Relativamente à evolução destes parâmetros entre o início e o fim do estudo, será de realçar o grande aumento no número de participantes na actividade física aeróbica, assim como a redução muito significativa nos consumos de álcool e tabaco.

Considerando a análise das patologias observadas, as mesmas foram distribuídas pelos respetivos grupos nosológicos de doenças: cerebrovasculares, cardiovasculares, do metabolismo e doenças do comportamento. Propusemo-nos verificar o resultado dos tratamentos efetuados, considerando para o efeito as terapêuticas realizadas agrupadas nos respetivos grupos terapêuticos.

Os nossos resultados, permitem concluir pela importância da determinação da Lp(a) como biomarcador de risco vascular de primeira linha, sendo que este foi o primeiro estudo que documentou a correlação significativa entre valores elevados de Lp(a) e todos os marcadores de risco vascular, nomeadamente e também com a esteatose hepática não alcoólica.

Face aos resultados obtidos, consideramos que a Lp(a) deverá ser integrada na avaliação bioquímica de rotina, em particular no rastreio do risco vascular, permitindo um diagnóstico precoce com consequente ponderação do risco. Sendo que é transversal a todas as idades e, por isso fundamental na prevenção primária permitindo um diagnóstico, intervenções adequadas e precoces. Este pressuposto não se aplica aos demais scores de cálculo e estratificação de risco cardiovascular a 10 anos que, para se determinar, incluem no seu cálculo a idade (> 30 anos), sexo, hábitos tabágicos, a pressão arterial, os lipídeos e vários outros FRCV (diabetes, hipertensão) condicionando uma intervenção precoce e adequada em doentes com elevado risco cardiovascular e metabólico apesar da idade.

Poderemos acreditar que a fénix renasceu das cinzas[1] considerando a importância e utilidade dos resultados obtidos e, tendo em conta as terapêuticas realizadas durante o estudo, pudemos por isso constatar que a Lp(a) deverá constituir um alvo terapêutico enquanto indicador e protagonista na gravidade do risco vascular[2].

Doravante e em prevenção primária, devem ser consideradas e aplicadas precocemente todas as terapêuticas dirigidas aos diversos FRCV, no sentido de adiar a inexorável evolução do processo aterosclerótico. Na primeira linha terapêutica e por ordem de importância, aparecem as estatinas, seguidas dos antiagregantes plaquetários, do alopurinol e da terapêutica antidepressiva. Dever-se-ão considerar sempre que necessário e adequadas à situação clínica, as terapêuticas com: antagonistas dos canais cálcio (ACC), inibidores da enzima conversora da angiotensina (IECA), antidiabéticos orais (ADO) e antagonistas dos recetores da angiotensina II (ARA-II). Como adjuvante terapêutico, é fundamental a adesão a estilos de vida saudáveis, melhorando o prognóstico relativamente à contenção e controlo do processo aterosclerótico.

INTRODUÇÃO

A Lp(a) é uma partícula semelhante à LDLc sintetizada pelo hepatócito e, consiste numa apolipoproteina B-100 que contém uma ligação covalente com a apolipoproteina (a) por uma ponte dissulfito em Kringle IV tipo 9(KIV-2) no local próximo da ligação ao recetor de LDL da apoB[3].

A Lp(a) está enriquecida de fosfolípidos oxidados sendo o seu maior transportador e daí as inerentes propriedades pro-inflamatórias. A Lp(a) compete com os sítios de ligação do plasminogénio resultando no decréscimo da síntese de plasmina e inibição da fibrinólise, sendo que o sistema fibrinolítico é um dos principais mecanismos de defesa na prevenção da trombose intravascular e do processo aterosclerótico.

A função "fisiológica" da Lp(a) não está esclarecida mas é consensual a importância das suas propriedades aterogénica, trombogénica e pró inflamatória, decisivas no contexto de implementação e desenvolvimento do processo aterosclerótico e da DCV.

Cerca de 1/4 da população mundial terá concentrações de Lpa (>30 mg/dl) que em estudos epidemiológicos tem vindo a ser associada a elevado risco de doença cardiovascular (DCV)[3].

Varias meta análises realizadas em prevenção primária e secundária, demonstraram que apesar da terapêutica com estatinas e consequente redução do LDLc, os valores elevados de Lp(a) estão associados a elevado risco de DCV.

A Lp(a) é um FRCV independente[1, 4], cuja determinação é proposta pelas *guidelines*[5] no sentido da sua avaliação regular em todos os doentes, com risco vascular intermédio[5]. Contudo, em nenhuma situação se propõe qualquer intervenção terapêutica específica dirigida à Lp(a) elevada, seja pela ausência alternativas específicas, como pela falta de propostas terapêuticas com evidência comprovada[6]. Apesar disso, estudos muito recentes sugerem que níveis elevados de Lp(a) só em conjugação com valores elevados de LDLc determinam a "agressividade aterogénica" da Lp(a) enquanto FRCV[4]. Mais se refere que, com valores séricos reduzidos de LDLc resulta numa importante atenuação da atividade aterogénica e consequente diminuição da "agressividade" da Lp(a)[6], ainda que esta persista em valores elevados. Trabalhos recentes como o *European Prospective Investigation of Cancer-Norfolk* (EPIC)-Norfolk[6, 7] e o *Copenhagen City Heart Study* (CCHS)[6] realizados em prevenção primária, enfatizam a importância perniciosa na conjugação de valores elevados da Lp(a) e LDLc, relevando a importância na redução do LDLc e consequentemente atenuação do risco cardiovascular (RCV) sendo certo que, a perceção deste facto já existia aquando da realização do estudo Júpiter [8-10].

Apesar de todos os esforços desenvolvidos na prevenção primária e secundária, a DCV isquémica continua a liderar as causas de morbilidade e mortalidade no mundo. A Lp(a) está intimamente associada à elevada mortalidade cardiovascular (CV). As mortes por DCV são a causa mais comum de morte prematura na raça branca de média idade na população Europeia [3, 7, 11, 12]. A Lp(a) distingue-se entre outros do tabagismo e diabetes porque ambos estão associados ao aumento do

risco CV e risco não CV[3]. O aumento das concentrações plasmáticas de Lp(a), está significativamente associado ao risco de doença arterial coronária[11]. Vários estudos indicam que, se a estratégia passar por definir a Lp(a) como alvo terapêutico[2] que poderá constituir-se como o único meio para reduzir o risco cardiovascular residual[13].

Ao longo dos tempos foram várias as intervenções terapêuticas entretanto propostas mas de utilidade muito limitada quando dirigidas à Lp(a), sendo que algumas delas foram mesmo abandonadas como no caso dos Fibratos demonstrando-se a sua ineficácia, terapêuticas de substituição hormonal (TSH) e, da Niacina (próxima da vitamina B6), que apesar de reduzir a Lp(a) em cerca de 30% apresentou efeitos adversos vários e indesejáveis.

Entre as terapias mais atuais e praticamente todas em fase "avançada" de investigação relativamente à sua eventual eficácia relativamente à Lp(a), devemos destacar os Inibidores do CETP, cujo mecanismo de ação não está claro e ainda se encontra longe de constituir uma eventual indicação terapêutica considerando alguns dos seus efeitos laterais adversos; os Inibidores da PCSK9, que apresentam reduções de Lp(a) entre 25-30%, cujo mecanismo de ação se mantem controverso podendo mesmo conduzir à formação de imunocomplexos no interior dos macrófagos e daí poder advir alguns riscos. As recentes terapêuticas, do grupo das terapias biológicas e com anticorpos monoclonais, destaque para os ApoB Antisense-oligonucleotidos (Mipomersen) e, o Apo(a) Antisense-oligonucleotidos em que o essencial da sua ação consiste em ligar-se diretamente ao mRNA da apolipoproteina (a), no núcleo dos hepatócitos inibindo assim a sua síntese. A Aferase de lípidos, tem permitido excelentes resultados na redução da Lp(a) conseguindo-se reduções nos seus níveis entre 60 - 70% sendo que estes resultados são dose dependente, mas a sua expressão terapêutica é muito reduzida também pelas suas indicações terapêuticas restritas.

A elevação de Lp(a) é um fator de risco independente causal para a DCV, sendo que este risco se torna particularmente elevado quando os doentes apresentam simultaneamente, valores elevados Lp(a) e de LDLc [6] aumentando de forma significativa a incidência da doença arterial coronária[12].

OBJETIVOS

Face ao antes exposto, constituiu nosso propósito revisitar a Lp(a) no contexto do risco vascular, em prevenção primária em doentes com dois ou mais FRCV pessoais e/ou familiares, que frequentassem com regularidade a consulta de Metabolismo e Risco Vascular há pelo menos 2 anos. Propusemo-nos abordar e diagnosticar precocemente o risco vascular e, se os resultados o permitissem, dar o nosso contributo para agilizar o cálculo do risco cardiovascular considerando para o efeito outro biomarcador, que não dependente de pressupostos inferidos da prevenção secundária. Avaliamos a relação entre a Lp(a) com o risco cardiovascular individual calculado pelos algoritmos atuais e mais em uso (FRS, AS-CVD, SCORE) com cálculo do risco CV a 10 anos. Propusemo-nos esclarecer potenciais efeitos benéficos da adequação no perfil lipídico e metabólico, com a eventual repercussão na evolução da Lp(a), em particular na sua "agressividade aterogénica" relativamente ao LDLc.

Avaliar a eficácia das estratégias terapêuticas implementadas ao longo do estudo e, aquilatar das respetivas consequências nomeadamente analisando os resultados considerando eventuais e potenciais sinergias farmacológicas e bioquímicas.

Outro objetivo estruturado e delineado no âmbito deste estudo consistiu no propósito de realizar a avaliação da qualidade de vida dos doentes à data de conclusão do estudo. Sendo que este objetivo constituiu critério de admissão e inclusão dos doentes que teriam de responder aos inquéritos SF-36v2 (aferido para a população portuguesa) e ao 15D pela facilidade de resposta direta e objetiva considerando o nível escolar e cultural dos nossos doentes.

MATERIAL E MÉTODOS

Estudo longitudinal e observacional que incluiu 516 doentes num universo dos 1677 indivíduos, observados e orientados com regularidade trimestral desde há pelo menos dois anos numa consulta de Metabolismo e Risco Vascular e que cumpriam todos os critérios de inclusão estabelecidos: ser portador de dois ou mais FRCV pessoais e/ou familiares, frequência regular e trimestral há pelo menos dois anos na Consulta de Metabolismo e Risco Vascular, em prevenção primária.

O protocolo de estudo, todas as informações detalhadas sobre a proveniência dos doentes e respetivo seguimento, eventuais financiamentos e, todos os documentos usados no mesmo tinham sido entretanto apresentados para apreciação, avaliação e decisão da Comissão de Ética para a Saúde do Hospital de S. João que deu o seu parecer favorável ao projeto em 30 de Setembro de 2010.

Decorrido este passo decisivo, remetemos por via postal para os 1677 doentes que cumpriam os critérios de seleção, a explicação escrita e detalhada sobre todos os objetivos pretendidos, juntamente com os documentos indispensáveis para inclusão no estudo (Declaração de consentimento, inquéritos SF-36v2 e 15 D), com total garantia do respetivo sigilo. O Consentimento Informado teria de ser assinado pelo doente mas, em caso de impossibilidade, deveria ser assinado pelo familiar que o acompanha com mais regularidade em consulta, dando o consentimento para utilização dos seus registos clínicos de interesse para o estudo com garantia de total sigilo.

Assim e para efeito de admissão no estudo, todos os doentes receberam informação detalhada oral e por escrito sobre o trabalho de investigação para efeitos do Consentimento informado, com identificação do Investigador Principal, do Orientador e dos Co-Orientadores (documentos que constituem o projeto de Tese avaliado em Setembro de 2014), em simultâneo tinham de preencher de forma anónima dois inquéritos sobre qualidade de vida 15D e SF-36v2 enquanto parte integrante do estudo. Assinada e entregue a Declaração de consentimento, elaborada em conformidade com a "Declaração de Helsínquia" da Associação Médica Mundial, juntamente com os respectivos inquéritos sobre a qualidade de vida, ficaram nesse momento incluídos no estudo, passando-se de seguida a respetiva colheita dos dados com interesse para investigação. O estudo decorreu entre 1995 e 2015 período que foi determinado pela cadência na entrega do consentimento informado assinado juntamente com os respetivos inquéritos, teriam de ser devolvidos de forma anónima e por via postal para o que se incluiu o respetivo envelope com porte pago e sem qualquer custo para o doente ou seu familiar.

Convém enfatizar que este processo terá sido dos mais difíceis e morosos, por isso condicionou e dilatou o tempo de observação para efeitos de investigação. Em Abril de 2015 e considerando o longo tempo já decorrido decidimos dar por encerrado o processo de admissão e inclusão, sendo que à data haviam sido recebidas as respostas dos 516 doentes (30,77%) do universo de 1677 com critérios de admissão.

Com a receção dos documentos solicitados, o doente foi de imediato admitido no estudo e consequentemente dada por concluída a observação para efeitos de investigação na data de receção dos documentos, procedendo-se de seguida à consequente recolha e tratamento dos dados de acordo com o protocolo.

Assim e sempre em conformidade com o protocolo de estudo, através do qual nos propusemos avaliar a evolução clínica e bioquímica, incluindo a observação e registo dos exames realizados e relevantes para o estudo, nomeadamente aqueles referentes à área cardiovascular: Eletrocardiograma de doze derivações (ECG), Ecocardiograma Modulo M bidimensional com cálculos de fração de ejeção, *Doppler* carotídeo e vertebral com determinação da espessura da íntima media (IMT), Monitorização ambulatória da pressão arterial (MAPA), Eletrocardiograma de 24 horas (*Holter*) entre os demais realizados de acordo com a patologia do doente, com destaque para a ecografia abdominal para a avaliação da morfologia hepática.

Os critérios para recolha e registo de dados e dos respetivos exames realizados reportaram-se àqueles efetuados aquando da primeira consulta e, do respetivo "*follow-up*" decorrido um ano, dois anos, 3 anos e, na conclusão do estudo individual com os resultados atuais realizados até à data de inclusão no estudo. Momento que determina para efeitos de investigação a inclusão do doente no estudo e conclusão da sua observação para o efeito.

Como antes já referimos, foi desde sempre nossa pretensão avaliar a qualidade de vida (QoL) dos doentes à data de conclusão do estudo, sendo que era condição de admissão dos doentes responder aos respetivos inquéritos. Estes resultados estão determinados, trabalhados e tratados mas não foram considerados para o presente trabalho.

O estudo é longitudinal e observacional incluiu 516 doentes do universo inicial de 1677 indivíduos, observados em prevenção primária, em consultas de periodicidade trimestral, frequentadas com regularidade há pelo menos dois anos entre 1995 e 2015 e sem qualquer evento cardiovascular conhecido. Todos os pacientes aceitaram e assinaram o respetivo consentimento informado assim como responderam aos dois inquéritos propostos para avaliação final da sua qualidade de vida.

Efetuou-se a avaliação e caracterização da amostra, observada da situação social, demográfica e económica dos doentes, incluindo o seu desempenho e situação perante a sua atividade profissional de acordo com o disposto e classificação usada pelo Instituto Nacional de Estatística (INE) de 2010 relativamente as profissões.

Caraterização e registos dos parâmetros antropométricos como o peso, estatura e calculo do índice de massa corporal (IMC) individual, perimêtros braquial e abdominal, prega cutânea tricipital (PCT), para alem da avaliação clínica, bioquímica e cardiovascular. A avaliação da morfologia hepática, foi realizada por ecografia/ultrassonografia em 509 doentes.

Efectuado o registo detalhado de todos os diagnósticos realizados, efectuando-se de seguida o agrupamento das doenças pelos respectivos grupos nosológicos: doencas cardiovasculares, do metabolismo, cerebrovasculares e doenças do comportamento.

Registo de todas as terapêuticas realizadas individualmente durante todo o estudo, com identificação e posologias detalhadas, posteriormente estruturadas e agrupadas nos respetivos grupos terapêuticos para efeitos de avaliação e repercussão das mesmas nos resultados em análise.

Determinação e calculo do risco vascular em todos os doentes através dos algoritmos mais em uso: *Framingham risk score* (FRS), *atherosclerotic cardiovascular disease* (ASCVD) - AHA/ACC e, *systematic coronary risk evaluation* (SCORE)-ESC, para doentes de baixo risco indicado para a população Portuguesa, como de elevado risco vascular.

Registo de todas as ocorrências de eventos no decurso do estudo.

ARTIGOS

ARTIGO 1

LIPOPROTEIN (A) IN THE ROUTINE EVALUATION OF CARDIOVASCULAR RISK IN THE PORTUGUESE POPULATION

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Lipoprotein (a) in the Evaluation of Cardiovascular Risk in the Portuguese Population
Lipoproteína (a) na Avaliação do Risco Cardiovascular na População Portuguesa

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Disclaimers: None declared.

Header: Lipoprotein(a) as an indicator of vascular risk.
Lipoprotein(a) in the routine evaluation of cardiovascular risk in the Portuguese population

Lipoprotein (a) in the Evaluation of Cardiovascular Risk in the Portuguese Population

Lipoproteína (a) na Avaliação do Risco Cardiovascular na População Portuguesa

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ABSTRACT

Introduction: High values of lipoprotein (a), related to atherosclerosis progression, are often considered a marker of thrombosis. We assessed the lipoprotein (a) profile in a group of patients with high vascular risk and no cardiovascular events, established its correlation with other cardiovascular risk factors and inferred the results for patients with metabolic disorders and, at least, two risk factors.

Material and Methods: This longitudinal observational study included 516 patients, who had at least two cardiovascular risk factors and regularly attended, for at least two years, the outpatient consultations at a clinic of metabolism and vascular risk for primary prevention. Sociodemographic, clinical and anthropometric parameters were obtained at the baseline visit. Hepatic morphology was assessed in 509 patients (98.6%) by ultrasonography. The 10-year vascular risk was estimated using Framingham risk score, atherosclerotic cardiovascular disease and systematic coronary risk evaluation tables.

Results: Significant correlations were found between lipoprotein (a) levels and the addressed vascular risk factors, as well as between lipoprotein (a), and Framingham risk score, atherosclerotic cardiovascular disease and systematic coronary risk evaluation charts. Lipoprotein (a) values were also considerably higher in patients with steatosis.

Discussion: Increased lipoprotein (a) values were directly associated with all markers of cardiovascular risk and with non-alcoholic hepatic steatosis.

Conclusion: Due to its high availability and low cost, lipoprotein (a) should become part of the routine evaluation of patients at vascular risk.

Keywords: Atherosclerosis; Cardiovascular Diseases; Lipoprotein (a); Portugal; Primary Prevention

RESUMO

Introdução: Valores elevados de lipoproteína (a), relacionados com a progressão da aterosclerose, são frequentemente considerados marcadores de trombose. O perfil de lipoproteína (a) foi avaliado num grupo de doentes sem eventos cardiovasculares mas com elevado risco vascular, estabelecendo-se a correlação com outros fatores de risco cardiovascular e inferindo-se os resultados para doentes com alterações metabólicas e, pelo menos, dois fatores de risco vascular.

Material e Métodos: Este estudo observacional longitudinal incluiu 516 doentes com, pelo menos, dois fatores de risco cardiovascular e que frequentavam, regularmente e há pelo menos dois anos, a consulta ambulatória de metabolismo e risco vascular para prevenção primária. Os parâmetros sociodemográficos, clínicos e antropométricos foram recolhidos na primeira visita. A morfologia hepática foi avaliada por ultrassonografia em 509 doentes (98,6%). O risco vascular a 10 anos foi estimado através de tabelas de cálculo de risco de Framingham, doença cardiovascular e risco coronário sistemático.

Resultados: Foram encontradas correlações significativas entre os níveis de lipoproteína (a) e os fatores de risco vasculares analisados, assim como entre lipoproteína (a) e as escalas de risco de Framingham, doença cardiovascular e risco coronário sistemático. Os valores de lipoproteína (a) apresentaram-se mais elevados em doentes com esteatose.

Discussão: Os valores elevados de lipoproteína (a) estão diretamente associados com todos os marcadores de risco cardiovascular e com esteatose hepática não alcoólica.

Conclusão: Como tal, considerando a sua elevada acessibilidade e custo reduzido, o marcador lipoproteína (a) deverá ser integrado na avaliação de rotina de doentes com risco vascular.

Palavras-chave: Aterosclerose; Doenças Cardiovasculares; Lipoproteína (a); Portugal; Prevenção Primária

INTRODUCTION

Atherosclerosis remains the major cause of death and premature disability in developed societies.[1] Current predictions estimate that by 2020 cardiovascular diseases (CVD),[2] particularly atherosclerosis, will become a global leading cause of death.[3] Lipoprotein (a), or Lp(a), is identical to the low-density lipoprotein cholesterol (LDLc), with the addition of apolipoprotein A (apoA), a highly glycosylated protein.[4,5] Lp(a) is often considered a marker of thrombosis, similarly to plasminogen, and a risk factor for CVD.[6] The cholesterol present in LDLc accounts for more than half of plasma cholesterol, in most individuals. Approximately 70% of the circulating LDLc is cleared by LDL-receptor-mediated endocytosis in the liver. ApoA is synthesized in the liver and attached by disulphide linkage to apoB-100, a structural protein of Lp(a). Also, apoB is the main structural protein of chylomicrons.[2] The human liver produces apoB-100, whereas the intestine produces apoB-48. Clearance of Lp(a) occurs mainly through the liver, but the uptake pathway is still unknown.[7] Nevertheless, Lp(a) is recognized as a strong risk factor for aortic and mitral stenosis in peripheral artery

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disease and might present other functions, including an important role in the association between atherosclerosis and thrombosis. [8,9]

Portugal is a Southern European country where CVD are the first cause of mortality and stroke incidence is higher compared to other European countries.[10] In this context, we assessed the levels of Lp(a) in Portuguese patients, who regularly attended outpatient consultations at the clinic of metabolism and vascular risk, over a two-year period. In addition, those patients had metabolic disorders and, at least, two cardiovascular risk factors (CVRF), but no previous cardiovascular events. Thus, the aim of this study is to determine the mean values of Lp(a) in the sample of patients and to infer the use of Lp(a) as an indicator of vascular risk in the Portuguese population with metabolic disorders and, at least, two CVRF.

MATERIAL AND METHODS

The longitudinal observational study included 516 patients, as a random sample of a universe of 1677 patients from an outpatient setting at a clinic of metabolism and vascular risk. Inclusion criteria were defined for those patients without cardiovascular events having, at least, two family or personal CVRF and attending an outpatient consultation about metabolism and vascular risk for primary prevention, for at least two years (between 1995 and 2015), on a quarterly periodicity. All patients accepted and signed the informed consent form. The protocol used in this study was approved by the local Ethics Committee of the São João Hospital Center. All procedures conducted in this study comply with the Declaration of Helsinki.

Patients were assessed for sociodemographic data, including their professional status, in accordance with the 2010 classification, by the Portuguese National Statistics Institute (Instituto Nacional de Estatística, INE). Afterwards, clinical characterization of the study participants was determined, at baseline, by anthropometric, biochemical and cardiovascular evaluation. The following tests were conducted: electrocardiogram (ECG), two-dimensional echocardiogram with ejection fraction calculation, and doppler ultrasonography of the supra-aortic trunks with evaluation of the carotid intima-media thickness (IMT). In addition, liver morphological changes were evaluated by ultrasonography. For classification of alcohol consumption, the following criteria were used: never; moderate, if one or two drinks daily; excessive, if three drinks daily; alcoholism; and abstinence, if at least a year had passed since the last drink. Evaluation of vascular risk was performed considering the three most used scores: Framingham risk score (FRS), atherosclerotic cardiovascular disease (ASCVD) - AHA/ACC,[11] and systematic coronary risk evaluation (SCORE)-ESC.[7]

Results were summarized as mean, median and standard deviation or count and percentage, for characterization of the study population. Normality distribution of data was assessed by the usual methodology used for validation (i.e., Kolmogorov-Smirnov test and Shapiro–Wilk test). For quantitative comparison of two independent groups, we used the *t*-test for independent samples or the Mann-Whitney non-parametric test, depending on the assumptions' validation by the statistical test. Spearman's correlation coefficient (SCC) was used to assess the relationship between two quantitative variables, in case the normality assumption was not verified. Regarding the sample distribution by age groups, we used the Kruskal-Wallis (KW) non-parametric test, instead of ANOVA F-test, whenever the distributions within groups presented relevant deviations from normality. The KW test allowed a comparative analysis between three or more independent groups and a quantitative or ordinal variable (as the dependent variable). Bonferroni correction for multiplicity of testing was used to verify age groups contrast [α' = 0.005, for α (0.05)/k (10 tests)]. All statistical tests were 2-tailed considering a significance level of 5%. The statistical analysis was conducted using the software IBM® SPSS® Statistics 19.

RESULTS

Sociodemographic parameters at first consultation

Most of the patients were women (56.6%) and Caucasian (98.6%). The patients' median age was 46 years. Regarding the educational background, 76.6% of the patients did not complete the third cycle; of those, 60.5% completed only the first cycle. Concerning the professional status, 72.5% of the patients were active and 13.2% were retired but still working. Among those actively employed patients, 40.5% had elementary occupations, 17.6% were skilled industrial, construction or craft workers and 17.4% were personal, protection or security service workers or sales workers.

Anthropometric and clinical evaluation

The median weight was 75.3 kg (range: 7.75 - 125.6 kg), while the median body mass index (BMI), calculated in kilogram per square meters, was 28.57 (range, 16.53 - 47.63 kg/m²). Amongst the study population, 25.0% had normal weight and 36.0% excess weight (BMI, 25 - 29 kg/m²). Moreover, 26.2% of patients had grade I obesity (BMI 30 - 34 kg/m²), 9.9% grade II obesity (BMI 5 - 39 kg/m²), 2.5% grade III obesity (BMI 40 - 44 kg/m²) and 0.4% morbid obesity (BMI ≥ 45 kg/m²). The abdominal (waist-to-hip) circumference (AC) had a median of 94 cm (range: 44 - 138 cm) and the average triceps skinfold (TSF) was 2.51 ± 1.13 cm (range: 0.3 - 5.0 cm; median: 2.4 cm).

Regarding cardiovascular evaluation, the average systolic blood pressure (SBP) was 145.52 ± 30.29 mmHg (range: 78 - 300 mmHg) with a median of 144 mmHg. The average diastolic blood pressure (DBP) was 87.91 mmHg (range: 42 - 148 mmHg) with a median of 90 mmHg. In addition, the average heart rate was 88.98 ± 11.79 bpm (range, 50 - 170 bpm) with a median of 90 bpm. Overall, 50.6% of patients had normal cardiac auscultation.[12]

Concerning the lifestyle and patients' habits, 66.0% had a moderate alcohol consumption, ranging from one (20.8%) to two daily drinks (45.2%), whereas 15.5% showed an excessive alcohol consumption. Alcoholism was diagnosed in

7.0% of patients and abstinence in 0.4%. Moreover, 71.9% did not practice regular physical activity, while 75.4% were non-smokers, 11.6% were ex-smokers and 13.0% were smokers.

In terms of the liver morphological evaluation, changes were detected through ultrasound in 509 patients (98.6%). Briefly, a pattern of hepatic steatosis was found in 435 patients (85.4%), of which 208 (40.8%) had associated hepatomegaly. Only 5.6% of patients presented changes in liver function tests.

Vascular risk calculations

The 10-year vascular risk was estimated based on the most commonly used vascular risk scores. For the FRS (30 - 74 years), applied to 436 patients, we obtained an average of 36.57 ± 26.37 (median: 32.60; range: 1.10 - 99.5), while for ASCVD (40 - 79 years), applied to 338 patients, the average was 24.83 ± 20.61 (median: 20.61; range: 0.86 - 95.69). As for the SCORE low-risk algorithm (45 - 64 years), 202 patients were assessed, obtaining an average of 3.24 ± 3.81 (median: 2.23; range: 0.09 - 27.63).

Thus, both ASCVD and FRS scores revealed a high median value for the estimated vascular risk, at 10 years, whereas the SCORE low-risk algorithm indicated a moderated median value.

Laboratory values

Laboratory parameters assessed at the first consultation are described in Table 1. Briefly, a relevant increase of C-reactive protein (CRP), fibrinogen, homocysteine and Lp(a) were observed. HDLc showed a median value of 29.00 mg/dl (min: 11.00 mg/dL), while a median value of 172.00 mg/dL (max: 299 mg/dl) was obtained for LDLc. The average CRP was 1.15 ± 1.01 (min-max: 0.5 - 9.7 mg/dL), with a median value of 0.80 mg/dl. An average value of 7.14 ± 2.80 (min-max: 2.1 - 16 mg/dL) was found for uric acid. Urinary albumin excretion (UAE) showed a median rate of 15.80 mcg/min/24 h (min-max: 0.5 - 459 mcg/min/24h). Furthermore, the median value for homocysteine was 21.00 mmol/L (min-max: 7.0 - 44.0 mmol/L) and the average Lp(a) was 62.57 ± 21.64 (min-max: 9.9 - 110 mg/dL), with a median value of 59.00 mg/dL. Overall, normal laboratory values for Lp(2) (i.e., < 30 mg/dL) were found in 25 patients (4.9%), while abnormal values were detected in 484 patients (95.1%).

Association of independent variables and Lp(a)

Firstly, we confirmed that our study population did not follow a normal distribution, thus, only non-parametric models were applied. As shown in Table 2, a high positive and significant correlation was detected between the Lp(a) and the following variables: IMT (r_s = 0.575), LDLc (r_s = 0.457) and homocysteine (r_s = 0.565), and a negative and weak correlation with HDLc (r_s = -0.111). Moderate, but also significant, correlations were found for CRP (r_s = 0.354), abdominal circumference (r_s = 0.335), Hb A1c (r_s = 0.307), and weak correlations for BMI (r_s = 0.276) and fast insulin (r_s = 0.210).

By using the Mann-Whitney test, a significant relationship between Lp(a) and hepatic steatosis was obtained (p < 0.001). This association corresponded to 435 (85.4%) patients with hepatic steatosis (median of 65.00, range: 10.0 - 110.0; average: 66.29 ± 20.11) *versus* 74 (14.5%) patients without hepatic steatosis (median of 39.00, range: 9.9 - 110.0; average: 40.73 ± 16.98).

Table 1 - Laboratory parameters, at first consultation

Parameters	n	Omitted by missing	Mean ± SD	Median	Range
CRP (mg/dL)	514	1	1.15 ± 1.01	0.80	[0.5;9.7]
HbA1c (%)	494	22	6.47 ± 1.97	5.90	[3.1;13.6]
Fructosamine (mmol/L)	398	118	263.89 ± 116.86	201.00	[114;601]
Fast insulin (micro units/mL)	481	35	13.48 ± 7.62	12.00	[0.8;67]
Peptide C (ng/mL)	486	30	2.57 ± 1.21	2.20	[0.2;9.4]
Total cholesterol (mg/dL)	516	0	278.69 ± 61.40	287.00	[98;457]
HDLc (mg/dL)	516	0	29.59 ± 11.76	29.00	[11;134]
LDLc (mg/dL)	516	0	171.20 ± 39.01	172.00	[39;299]
VLDLc (mg/dL)	516	0	30.81 ± 22.33	24.00	[7;294]
Triglycerides (mg/dL)	515	1	186.27 ± 133.245	147.00	[18;1506]
Fibrinogen (mg/dL)	487	29	369.26 ± 96.05	369.00	[89;651]
Homocysteine (mmol/L)	509	7	20.82 ± 5.27	21.00	[7.9;44]
LP(a) (mg/dL)	509	7	62.57 ± 21.64	59.00	[9.9;110]
≤ 30 (normal)	25	0			
> 30 (abnormal)	484	0			
Uric acid (mg/dL)	516	0	7.14 ± 2.80	7.15	[2.1;16]
Microalbuminuria 24h (mcg/min)	499	17	45.28 ± 68.33	15.80	[0.5;459]

CRP: C-reactive protein; HbA1c: hemoglobin A1c; HDLc: high density lipoprotein cholesterol; LDLc: low density lipoprotein cholesterol; VLDLc: very-low-density lipoprotein cholesterol; LP(a): lipoprotein(a)

Table 2 - Correlation between Lp(a) and the other clinical and biochemical parameters, at first consultation

Parameters	SCC	*p*
Lp(a) *versus* HDLc	r_s = -0.111	0.012
Lp(a) *versus* LDLc	r_s = 0.457	< 0.001
Lp(a) *versus* Fast insulin	r_s = 0.210	< 0.001
Lp(a) *versus* Hb A1c	r_s = 0.307	< 0.001
Lp(a) *versus* Abdominal circumference (waist-to-hip)	r_s = 0.335	< 0.001
Lp(a) *versus* Height	r_s = 0.009	0.842
Lp(a) *versus* BMI	r_s = 0.276	< 0.001
Lp(a) *versus* CRP	r_s = 0.354	< 0.001
Lp(a) *versus* Homocysteine	r_s = 0.565	< 0.001
Lp(a) *versus* IMT	r_s = 0.575	< 0.001

SCC: Spearman correlation coefficient (r_s); LP(a): lipoprotein(a); HDLc: high density lipoprotein cholesterol; LDLc: low density lipoprotein cholesterol; Hb A1c: hemoglobin A1c; BMI: body mass index; CRP: C-reactive protein; IMT: intima-media thickness

The association between Lp(a) and hepatic steatosis with hepatomegaly was also significant ($p < 0.001$). This analysis compared 208 (40.8%) patients with hepatomegaly (median of 77.90, range: 10.0 - 110.0; average: 74.90 ± 18.81) *versus* 301 (59.1%) patients with steatosis without hepatomegaly (median of 49.00, range: 9.9 - 105.0; average 54.05 ± 19.25).

Table 3 describes the results that were significant ($p < 0.001$), regarding the distribution of Lp(a) by age group, with patients older than 50 years, achieving higher median values of Lp(a). Multiple comparisons between age groups ($\alpha' = 0.005$) allowed to determine that all groups presented significant differences (< 20 years *versus* other age groups, [$p < 0.001$]; 20 - 34 years *vs* other age groups [$p < 0.001$]; 35 - 49 years *vs* 50 - 64 years [$p = 0.001$], 35 - 49 years *vs* ≥ 65 years [$p < 0.001$]), except for age groups of 50 - 64 years *vs* ≥ 65 years ($p = 0.540$).

A positive and significant correlation was found between Lp(a) and the vascular risk scores used in CVD stratification ($p < 0.001$), as shown in Table 4. Correlation between Lp(a) and cardiovascular risks was moderate, and high Lp(a) values were associated with high scores of those CV risks stratification tables (i.e., FRS, ASCVD and SCORE).

DISCUSSION

The main finding of this study was that average values of Lp(a) were increased in patients at high vascular risk and were directly correlated with other CVRF. These data constitute valuable information for clinical evaluation, allowing to infer about the adequate orientations and therapeutic interventions, based on the patients' personal and family history. Moreover, this observation can be employed to all three criteria presented for vascular risk calculation, including the SCORE low-risk algorithm, which is applicable to Portuguese patients.

A significant correlation was observed between Lp(a) and IMT, BMI, LDLc, homocysteine, CRP and abdominal circumference, as previously described.[13,14] The negative, weak significant correlation between Lp(a) and HDLc should also be highlighted. In addition, results regarding height were relevant if considering that the Portuguese population presents an average short height and individuals with pyknic morphology are more susceptible to CVD. Furthermore, the pro-inflammatory effect of Lp(a) is corroborated by its

Table 3 - Lp(a) distribution by age groups, at first consultation

Age groups	n	Mean ± SD	Median	Range
< 20	14	26.42 ± 15.87	29.00	[0.0;44.0]
20 - 34	104	47.86 ± 21.43	45.00	[0.0;110.0]
35 - 49	177	57.67 ± 25.98	56.00	[0.0;110.0]
50 - 64	144	63.64 ± 25.67	65.50	[0.0;102.0]
≥ 65	77	62.50 ± 26.89	69.00	[0.0;103.0]
KW (df): value, $p < 0.001$				

KW: non-parametric Kruskal-Wallis test; Lp(a): lipoprotein (a)

Table 4 - Correlation between Lp(a) and cardiovascular risk (10 years), at first consultation

Parameters	Spearman correlation r_s
Lp(a) *versus* FRS (30 - 74 years) Initial	0.458*
Lp(a) versus ASCVD (40 - 79 years) Initial	0.414*
Lp(a) versus SCORE (low-risk algorithm, 45 - 64 years) Initial	0.391*

FRS: Framingham risk score; ASCVD: atherosclerotic cardiovascular disease; SCORE: systematic coronary risk evaluation. * $p < 0.001$

correlation with the CRP.[15]

We also highlight the significant relationship between Lp(a) and hepatic steatosis ($p < 0.001$). Lp(a) values were considerably higher in patients with steatosis. Further studies are required to better understand the relationship in cases of non-alcoholic fatty liver disease (NAFLD) without secondary causes for steatosis, such as excessive alcohol consumption, virus infection or endocrine disorders.

Although results among adult patients are variable, age has been significantly associated with increased Lp(a).[16] Furthermore, besides that Lp(a) values increase with age, a significant difference between younger (20 - 39 years) and older (> 60 years) subjects has been described.[17] Therefore, we assessed the effect of age groups on the distribution of Lp(a), which showed that Lp(a) presented a significant association between age groups, except for the two groups of older patients (50 - 64 years *vs* ≥ 65 years; $p = 0.540$). Thus, an early perception of the vascular risk with an easy and adequate risk stratification in primary prevention should be provided.[18] This information presupposes an early reflection to restructure the intervention procedure, so that patients' mortality and cardiovascular morbidity are reduced. Also, the positive correlation between Lp(a) and vascular risk scores suggest that Lp(a) plays a key role in vascular risk estimation. This correlation should be considered when planning or re-evaluating therapy interventions, in terms of primary prevention.[18]

Lp(a) presents some unique features that enable it to enrich the atherosclerotic plaques of cholesterol. Additionally, this lipoprotein has been shown to increase smooth muscle cell migration and proliferation, chemotactic activity, endothelial adhesion molecule expression, foam cell formation and lipid-induced atherogenesis. Lp(a) particles accumulate in human atherosclerotic lesions in the same way as LDLc, but probably more easily, due to their greater affinity to the arterial wall than LDLc. For this reason, increased values of Lp(a) represent a CVRF and should be treated.[19,20]

Similarly to CVD, treatment of NAFLD is focused on reducing CVRF and resistance to insulin. Since well-established therapeutic options are still lacking, lifestyle modifications and treatment of individual risk factors are recommended.[21,22] Neverthless, albeit the known benefits of diet, followed by physical activity and adequate control of modifiable risk factors, it hasn't been demonstrated that those interventions have an impact on Lp(a) levels.[23] Considering the present results for the Portuguese patients, we can infer that, although the Mediterranean diet is an essential part of primary prevention,[24,25] it should not be overrated compared to other CVRF that have stronger associations with CVD and related consequences.[26,27] Therefore, the increased focus on the Mediterranean diet may have contributed to the postponing of more incisive interventions and therapeutic orientations that, if initiated early, could be decisive in reducing the burden of cardiovascular disease.[28,29]

Overall, Lp(a) is associated with conventional CVRF, including high levels of LDLc, and were found to be increased in patients with hepatic steatosis and those with high vascular risk. As such Lp(a) should be valued as a biomarker for an early initiation of therapy and intensive orientations for primary prevention of CVD.[18,20,23,30]

Finally, this study presents some limitations inherent to its design and observational nature. For instance, the interpretation of our results should account for possible within-subject variation and control variables (e.g., BMI, blood pressure and laboratory parameters, such as CRP or Hb Ac1), as well as omitted individuals (missing data), over the study period. Despite these limitations, this study provides us with unique data about the Lp(a) profile in Portuguese patients at high risk of vascular disease, with implications in current clinical practice.

CONCLUSION

In conclusion, Lp(a) is a strong indicator of vascular risk, directly correlated with all markers of cardiovascular risk and with non-alcoholic hepatic steatosis. Due to its high availability and low cost, Lp(a) should become part of routine evaluation of at-risk patients in the Portugal.

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PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

All authors report no conflict of interest.

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ARTIGO 2

LIPOPROTEIN (A) AS A KEY TARGET IN MULTIPLE THERAPEUTIC APPROACHES FOR CARDIOVASCULAR DISEASE

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Lipoprotein (a) as a key target in multiple therapeutic approaches for cardiovascular disease
Lipoproteína (a) como alvo fundamental nas estratégias terapêuticas múltiplas para a doença cardiovascular

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EDITORIAL COMMENT

Lipoprotein(a) as a novel therapeutic target for preventing cardiovascular disease: A whiter shade of pale?

Lp(a) como um novo alvo terapêutico na prevenção da doença cardiovascular: uma luz ao fundo do túnel?

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Research on the importance of lipoprotein(a) [Lp(a)] gained new momentum when it became a potential therapeutic target. Our understanding of this mysterious circulating lipoprotein particle has undergone advances and setbacks since its discovery in 1963 by Kåre Berg's group.[1]

Lp(a) is composed of liver-derived apolipoprotein A and apolipoprotein B-100, and has a similar structure to both low-density lipoprotein cholesterol (LDL-C) and plasminogen. Lp(a) thus has a proatherogenic and a prothrombotic component, and is associated with the pathogenesis of cardiovascular disease (CVD).

Findings from epidemiological, genetic and clinical studies[2–4] have provided compelling evidence establishing Lp(a) as a marker of increased CVD risk in both primary and secondary prevention, including myocardial infarction (MI), stroke, and calcific aortic valve disease (CAVD).

However, significant gaps in knowledge remain about the biology and pathophysiology of Lp(a). To address these gaps, a National Heart, Lung, and Blood Institute working group identified several challenges to fully understand the role of Lp(a) in CVD/CAVD.[5] These include its metabolism and pathophysiological mechanisms, how to measure it, current and emerging therapies for elevated Lp(a), and identification of patients at high Lp(a)-mediated risk.

Joaquim Meireles-Brandão carried out a single-center retrospective observational study, published in this issue of the *Journal*,[6] of 516 patients (224 male; 292 female; 98.6% Caucasian) with at least two cardiovascular risk factors who regularly attended outpatient consultations at a cardiovascular risk and metabolism clinic for primary prevention. The aim was to analyze the effect of combined standard pharmacological therapy along with lifestyle interventions for managing Lp(a) levels in patients at high cardiovascular risk but who had not suffered major adverse cardiovascular events. The patients were followed for a mean of 11.35±4.32 years.

The results show that, in this well-controlled population under different drug therapies (statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, oral antidiabetics, antiplatelets, calcium channel blockers and allopurinol) there was a reduction in Lp(a) values during the follow-up period.

There was also a significant association between Lp(a) and cardiovascular risk scores in patients with high vascular risk. In a previous work in the same population,[7] the author reported that increased Lp(a) levels were also strongly associated with cardiovascular risk factors, such as

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carotid intima-media thickness, LDL-C and homocysteine, as well as with non-alcoholic hepatic steatosis.

This study points to the need to measure Lp(a) in routine assessment of at-risk patients, because as a marker of cardiovascular risk, Lp(a) should be recognized as a therapeutic target. It may be useful to initiate combined drug therapies and to promote healthy lifestyles in primary prevention, targeting various cardiovascular risk factors, in order to delay the atherosclerotic process.

These results may lead to better identification of target populations who will benefit most from Lp(a)-lowering therapies.

Several other studies have addressed this question. Among them, the BiomarCaRE project[8] confirmed Lp(a) as a marker of cardiovascular risk in the European population, demonstrating increased cardiovascular risk for Lp(a) >50 mg/dl, which is in line with the target level of <50 mg/dl recommended by the guidelines. Further, it showed a north-south gradient of Lp(a) levels across Europe, with lower levels in northern European cohorts.

Another study in different ethnic groups worldwide also showed that high Lp(a) concentrations (>50 mg/dl) were associated with significantly increased risk of MI in all populations except Arabs and Africans.[9]

Nevertheless, Lp(a) is not routinely tested in clinical practice, and there is a widespread lack of awareness of its role in accelerating atherosclerotic CVD.

Which patient groups should be screened for Lp(a)? The European Atherosclerosis Society Consensus Panel[10] recommends that Lp(a) should be measured in patients with intermediate or high risk for CVD or coronary heart disease (CHD). In particular, those patients presenting with (i) premature CVD, (ii) familial hypercholesterolemia, (iii) a family history of premature CVD and/or elevated Lp(a), (iv) recurrent CVD despite statin treatment, (v) 3% 10-year risk of fatal CVD according to the European guidelines[11] and (vi) 10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines. The measurement needs to be taken only once per patient life, and repeated measurements of Lp(a) are only indicated if a treatment for elevated Lp(a) levels is initiated in order to monitor therapeutic response.[12]

Screening for elevated Lp(a) will enable standard preventative measures to be introduced, including optimal control of blood pressure, diabetes and LDL-C levels and smoking cessation, and in the future the use of novel therapies that effectively lower Lp(a). Several agents are currently in development to lower Lp(a), such as proprotein convertase subtilisin/kexin type 9 inhibitors, antisense oligonucleotides targeting apolipoprotein B, and microsomal triglyceride transfer protein inhibitors.[13–15]

Early detection and intervention, preferably before the onset of atherosclerotic CVD, offers the best opportunity to reduce the time-dependent risk associated with this important cardiovascular risk factor. However, it should not be forgotten that there is to date no strong clinical evidence that lowering Lp(a) has any beneficial effects in preventing cardiovascular disease.

Conflicts of interest

The author has no conflicts of interest to declare.

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ORIGINAL ARTICLE

Lipoprotein(a) as a key target in combined therapeutic approaches for cardiovascular disease

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Lipoprotein(a);
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Peripheral arterial disease

Abstract
Introduction and Objective: Lipoprotein(a) [Lp(a)] is an independent cardiovascular risk factor but is closely associated with other similar risk factors that are manageable with appropriate treatment and guidance. We aimed to study the impact of using combined therapy for managing Lp(a) levels in patients at high cardiovascular risk but without major adverse cardiovascular events, in primary prevention.
Methods: We conducted a retrospective observational study in 516 patients randomly selected from a group of 1677 patients who attended cardiovascular risk and metabolism consultations between 1995 and 2015. The disorders observed and therapies used were classified into nosological and pharmacological groups, respectively. Cardiovascular risk was calculated based on the Framingham risk score, the European Society of Cardiology's SCORE and the American College of Cardiology's ASCVD Risk Estimator, and changes in patients' lifestyle were assessed.
Results: Significant differences ($p<0.001$) were found in almost all metabolic variables, except fasting insulin and C-peptide. Lp(a) levels were also significantly reduced ($p<0.001$). Carotid intima-media thickness improved, decreasing from 2.90 mm to 1.40 mm; however, there was no reduction in the number of cases of vascular stenosis. Of patients with hepatic steatosis (85.5%), 40.7% presented hepatomegaly, but liver function was only altered in a few patients (14.5%). Lipid-lowering therapy, especially statins, significantly decreased Lp(a), benefiting from synergy with other treatments.
Conclusions: Lp(a) is a key overall indicator of vascular risk and should be considered a therapeutic target. Besides a healthy lifestyle, primary prevention should include combined drug therapies to address all cardiovascular risk factors and to delay the atherosclerotic process.
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PALAVRAS-CHAVE
Lipoproteína(a);
Doenças cardiovasculares;
Aterosclerose;
Terapêutica farmacológica combinada;
Risco cardiovascular;
Doença arterial periférica

Lipoproteína(a) como alvo fundamental nas estratégias terapêuticas múltiplas para a doença cardiovascular

Resumo
Introdução e objetivo: Lp(a) é um fator de risco cardiovascular independente, mas intrinsecamente associado a outros fatores de risco similares, controláveis com terapêuticas e orientações adequadas. O nosso objetivo é estudar o impacto do uso de terapêuticas combinadas na gestão da evolução da Lp(a) em doentes com elevado risco vascular, sem ECVM em prevenção primária.
Métodos: Estudo observacional retrospetivo realizado em 516 doentes, selecionados aleatoriamente de um universo de 1677 indivíduos, que participaram regularmente em consultas de risco vascular e metabolismo entre 1995 e 2015. As patologias observadas e terapêuticas utilizadas foram distribuídas em diferentes grupos nosológicos e grupos farmacológicos, respetivamente. Calculou-se o RV com base em FRS, SCORE e ASCVD e avaliou-se também a evolução do estilo de vida dos doentes.
Resultados: Encontraram-se diferenças significativas (p<0,001) em quase todas as variáveis metabólicas, exceto insulina (jejum) e péptido-C. Houve uma redução significativa nos níveis de Lp(a) (p<0,001). A espessura íntima-média carotídea evoluiu favoravelmente, diminuindo de 2,90 mm para 1,40 mm; porém, não houve redução do número de casos de estenose vascular. Dos doentes com esteatose hepática (85,5%), 40,7% apresentaram hepatomegalia. Contudo, poucos doentes (14,5%) apresentaram função hepática alterada. A terapêutica antidislipidémica, especialmente as estatinas, diminuiu significativamente a Lp(a), beneficiando da sinergia com demais tratamentos.
Conclusões: Lp(a) é um indicador global e fundamental de risco vascular, a considerar como alvo terapêutico. Além de um estilo de vida saudável, a prevenção primária deve incluir terapêuticas farmacológicas combinadas dirigidas aos fatores de risco cardiovasculares e, consequentemente, retardar o processo aterosclerótico.
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List of abbreviations

ACEI	angiotensin-converting enzyme inhibitor
AMBP	ambulatory blood pressure monitoring
ARB	angiotensin receptor blocker
apoA	apolipoprotein A
BMI	body mass index
CAD	coronary artery disease
CCB	calcium channel blocker
CRP	C-reactive protein
CVD	cardiovascular disease
FRS	Framingham risk score
HDL	high-density lipoprotein
IMT	carotid intima-media thickness
Lp(a)	lipoprotein(a)
LDL	low-density lipoprotein
MACE	major acute cardiovascular events
NAFLD	non-alcoholic fatty liver disease
OAD	oral antidiabetic
PAD	peripheral arterial disease
SCORE	Systematic Coronary Risk Evaluation
SSRI	selective serotonin reuptake inhibitors
TC	total cholesterol

Introduction

Lipoprotein(a) [Lp(a)] is identical to low-density lipoprotein (LDL) except for the addition of apolipoprotein A (apoA), which is highly glycosylated. There is a striking homology between the amino acid sequences of apoA and plasminogen, which is recognized to be a cardiovascular risk factor.[1] Thus, Lp(a) may play an important role in the transition from atherosclerosis to thrombosis, because it activates monocyte adhesion and migration of macrophage foam cells into the arterial wall.[2] Lp(a) is often considered a marker of thrombosis.[3]

Cardiovascular disease (CVD) is a major cause of death in patients with peripheral arterial disease (PAD). These patients also tend to suffer from complications when they have diabetes, dyslipidemia and hypertension. They may also develop severe systemic atherosclerosis, leading to increased mortality due to coronary artery disease (CAD).

High Lp(a) is positively associated with coronary artery calcification, CAD and PAD.[4,5] It also promotes thrombosis by binding to fibrin, thus blocking the fibrinolytic action of plasmin.[2] Lp(a) may be a predictor of peripheral and central CVD in younger men and women with dyslipidemia.

Several observations suggest that targeting Lp(a) could decrease total residual cardiovascular risk, as increased

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plasma Lp(a) concentrations are significantly associated with higher risk of CAD.[6]

Lp(a) is a marker of particular risk for poor outcomes in terms of severity and progression of CVD. Several prospective studies have correlated Lp(a) levels with vascular disease in general, and plasma Lp(a) >30 mg/dl with increased cardiovascular risk.[4]

Studies with statins alone reveal that, although they significantly reduce LDL and major adverse cardiovascular events (MACE), statins do not appear to reduce Lp(a) concentrations. Almost all studies in this field have targeted total cholesterol (TC) and LDL, as well as high-density lipoprotein cholesterol (HDL), but none has validated the use of HDL as a therapeutic target in the management of cardiovascular risk factors. Furthermore, in clinical practice cardiovascular risk scores are not usually applied to younger patients (aged <40 years) with lower HDL levels, even if they have other cardiovascular risk factors. We therefore aimed to assess the possible relevance of all lipid fractions, including HDL, to cardiovascular risk factors, regardless of age, and following current clinical guidelines.[7–9] In this study, we assessed clinical and biochemical changes in randomly selected patients with two or more cardiovascular risk factors, in primary prevention, with no known cardiovascular events, and considering their social, cultural and demographic characteristics, before and after the patients underwent treatment and medical guidance, and the impact on metabolism and lipid, C-reactive protein (CRP), fibrinogen and homocysteine levels, among other clinical parameters, including Lp(a) profile according to the criteria of the BiomarCaRE consortium.[10]

Methods

This retrospective observational study was conducted in 516 patients randomly selected from a group of 1677 patients who attended cardiovascular risk and metabolism consultations between 1995 and 2015, in primary prevention, and had not suffered MACE. The selection criteria were as follows: at least two personal and/or family cardiovascular risk factors, regular attendance at a three-monthly consultation for a minimum of two years, and an annual biochemical assessment, including cardiovascular exams and clinical assessment. Participants filled in a self-administered questionnaire and provided written informed consent for inclusion in the study, which was approved by the Ethics Committee of São João Hospital Center, Porto. Patients were followed for both clinical and anthropometric changes during the observation period, paying particular attention to lipid and metabolic profiles and variations in Lp(a) levels. The disorders diagnosed were classified into the following nosological groups: cardiovascular, cerebrovascular, metabolic and behavioral diseases. Data were collected from the first medical consultation until the last or current appointment recorded on the patient's medical chart. It was established that an individual patient's record could only be updated for specific reasons, such as CVD, dependency or immobility, MACE or death. Records were updated 19 times due to death and six times due to the patient being bedridden.

Patients' sociodemographic characteristics were analyzed based on their clinical records. Their clinical, anthropometric, biochemical and cardiovascular characteristics were also analyzed and recorded. These assessments included cardiovascular exams, including electrocardiogram (ECG), two-dimensional echocardiogram and Doppler ultrasound (7.5 mHz linear probe, Sonos 1000, Hewlett Packard, Andover, MA) of the supra-aortic trunks to measure carotid intima-media thickness (IMT), as well as ambulatory blood pressure monitoring (ABPM).

Assessment of both renal and liver function are essential to analysis of metabolic status and the effects of pharmaceutical therapy. Renal function was therefore assessed in this study, based on microalbuminuria and creatinine clearance estimated by the Cockcroft-Gault method, and liver function and morphology were assessed by ultrasound.

Cardiovascular risk was calculated based on the three most commonly used scores: the Framingham risk score (FRS), the European Society of Cardiology's Systematic Coronary Risk Evaluation (SCORE), and the American College of Cardiology's atherosclerotic cardiovascular disease risk estimator (ASCVD). The resulting overall scores were analyzed by age-group. Also, due to the association between metabolic compensation and clinical improvement in patients with cardiovascular risk factors, the study included assessment of patients' lifestyle behaviors, including alcohol consumption (classified as never, occasional, moderate [one or two drinks daily], excessive [three or more drinks daily], alcoholic, or abstinent [at least one year since the last drink]), smoking (current smoker, ex-smoker or never-smoker), and exercise levels (all aerobic exercise at least twice a week in addition to that arising from daily activities).

Finally, drug therapies administered during the observation period were classified into pharmacological groups.

Statistical analysis

Quantitative variables were summarized using descriptive statistics: mean, median, standard deviation and range (minimum and maximum). Categorical variables were expressed as absolute (n) and relative (%) frequencies. Associations between two categorical variables were tested using the chi-square test or Fisher's exact test. The McNemar test for paired samples was used to compare the presence of a symptom before and after treatment or to compare the results of two diagnostic tests applied in the same group. Quantitative variables in two independent groups were compared using the t test for independent samples or the Mann-Whitney (MW) non-parametric test, according to whether the respective assumptions were validated. The non-parametric Wilcoxon signed-rank (WSR) test and sign test (ST) were used for paired samples to compare clinical scores before and after treatment if the assumption of normality was not confirmed. Statistical tests were two-tailed and the significance level was taken to be 5%. Multivariate linear regression analysis was performed to assess associations

between variables of interest and changes in Lp(a) levels between the beginning and the end of the study period. Stepwise optimization was used to choose the statistically significant variables for the model. All statistical analyses were conducted using IBM® SPSS® Statistics version 19.

Results

Sociodemographic, clinical and anthropometric characteristics of the study population

Of the 516 patients, 224 were male and 292 were female, and 98.6% were Caucasian. The mean observation time was 11.35±4.32 years (range: 2-26), median 11.0 years.

During the observation period, patients' age increased from an initial median of 46 years to a final median of 58 years. Thus, age grouping was readjusted, as the number of patients decreased drastically in the <20 years (initial: 2.2%; final: 0.2%) and 20-34 years (initial: 20.2%; final: 7.0%) age groups, changed slightly in the 34-50 years age group (initial: 34.3%; final: 22.9%), and increased in the 50-64 years (initial: 27.9%; final: 35.5%) and ≥65 years (initial: 14.9%; final: 34.5%) age groups. By the end of the observation period, 23 patients had died (4.5%) and 41 patients were bedridden (7.9%); most of these events occurred after data collection.

Changes in patients' clinical and anthropometric assessments between initial and final observations are detailed in Table 1. Significant reductions were seen in waist circumference, upper arm circumference and triceps skinfold (p<0.001). In addition, there were considerable improvements in blood pressure control, reflected in statistically significant differences in mean systolic and diastolic daytime and night-time blood pressure (p<0.001). The number of patients with controlled atrial fibrillation rose from nine to 18 patients during the study period, while the number with non-controlled atrial fibrillation decreased from two to one. No statistical differences were found regarding weight, height or body mass index.

Table 2 Changes in patients' lifestyles between the initial and the final visits.

	n (%)	
	Initial	Final
Smoking		
Ex-smoker	60 (11.6)	90 (17.4)
Never-smoker	389 (75.4)	402 (77.9)
Current smoker	67 (13.0)	24 (4.7)
Alcohol consumption		
Never	57 (11.1)	251 (48.7)
Occasional	107 (20.8)	161 (31.3)
Regular/moderate (one or two drinks/day)	233 (45.2)	68 (13.2)
Excessive (more than two drinks/day)	80 (15.5)	17 (3.3)
Alcoholic (more than three drinks daily)	36 (7.0)	8 (1.6)
Abstinent (no drinks for at least one year)	2 (0.4)	10 (1.9)
Exercise		
Physically inactive	371 (71.9)	144 (28.0)
Physically active	145 (28.1)	371 (72.0)

Lifestyle

Table 2 shows changes in patients' lifestyles. The reduction in alcohol consumption and the unexpected increase in regular exercise should be noted.

Biochemical assessment

Table 3 reports the results of the biochemical assessments. Significant differences were found in almost every metabolic variable studied, including CRP, glycated hemoglobin, fructosamine, TC, HDL, LDL, very-low-density lipoprotein, triglycerides, fibrinogen, homocysteine, uric acid and microalbuminuria (p<0.001). In addition, fasting insulin

Table 1 Changes in anthropometric and clinical assessments between initial and final visits.

	n	Mean difference	Median difference	Range (min-max)	p
Weight, kg	516	-0.54±9.10	-0.4500	-40.00-57.60	0.069 (WSR)
Height, cm	516	-0.37±4.73	0	-6.00-86.00	0.700 (ST)
BMI, kg/m^2	516	-0.36±3.23	-0.19	-15.94-10.61	0.077 (ST)
Waist circumference, cm	516	-2.03±8.00	-2.00	-43.00-45.00	<0.001 (WSR)
Upper arm circumference, cm	516	-1.41±2.75	-2.00	-10.00-10.00	<0.001 (WSR)
Triceps skinfold, cm	516	-0.39±0.63	-0.35	-3.00-1.20	<0.001 (ST)
SBP, mmHg	516	-19.35±25.28	-18	-148.00-56.00	<0.001 (ST)
DBP, mmHg	516	-13.35±25.29	15.72	-80.00-30.00	<0.001 (ST)
Heart rate, bpm	493	-10.30±12.90	-10	-104.00-22.00	<0.001 (ST)
Daytime SBP, mmHg	478	-23.24±24.80	-22.50	-147.00-29.00	<0.001 (ST)
Daytime DBP, mmHg	478	-21.45±17.98	-22.00	-86.00-24.00	<0.001 (ST)
Night-time SBP, mmHg	478	-17.77±19.11	-17.00	-127.00-25.00	<0.001 (ST)
Night-time DBP, mmHg	478	-19.07±15.89	-18.00	-81.00-14.00	<0.001 (ST)

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; ST: sign test; WSR: Wilcoxon signed-rank test.

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Table 3 Changes in biochemical assessments between the initial and the final visits.

	n	Mean difference	Median difference	Range (min-max)	p (WSR)
CRP, mg/dl	508	-0.53±1.02	-0.10	-7.8-7.9	<0.001
HbA1c, %	484	-0.96±1.54	-0.40	-7.6-3.5	<0.001
Fructosamine, mmol/l	387	-71.25±103.16	-22.00	-379-123	<0.001
Fasting insulin, μU/ml	463	-0.53±6.08	0.00	-30-37.5	0.188
C-peptide, ng/ml	474	-0.09±1.06	0.00	-5.3-8.2	0.042
TC, mg/dl	516	-103.68±63.02	-101.00	308.00-88.00	<0.001
HDL, mg/dl	516	19.35±12.19	19.00	-74.00-60.00	<0.001
LDL, mg/dl	505	-75.60±40.80	-77.00	-224-59	<0.001
VLDL, mg/dl	509	-12.25±19.41	-6.00	-139-45	<0.001
Triglycerides, mg/dl	508	-69.77±114.52	-42.50	-968-144	<0.001
Fibrinogen, mg/dl	477	-64.43±73.99	-59.00	-412-292	<0.001
Homocysteine, mmol/l	499	-9.94±4.98	-9.00	-35-23	<0.001
Lp(a), mg/dl	499	-32.11±15.41	-30.00	-76-4.1	<0.001
≤30 (normal)	25				
>30 (abnormal)	484				
Uric acid, mg/dl	509	-2.31±2.31	-2.10	-9.5-3.3	<0.001
24-h microalbuminuria, μg/min	489	-29.87±50.94	-8.00	-283-80	<0.001

CRP: C-reactive protein; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LP(a): lipoprotein(a); TC; total cholesterol; VLDL: very-low-density lipoprotein; WSR: Wilcoxon signed-rank test.

and C-peptide values decreased between the first and the final observation, although without statistically significant differences. Lp(a) levels were also significantly reduced.

Cardiovascular exams

The cardiovascular exams performed included ECG, echocardiogram, IMT and ABPM.

Some changes were found in the ECG assessment. A normal exam was seen in 247 patients (47.2%) at the initial observation, compared to 281 patients (55.6%) at the final visit. Atrial fibrillation was present in four patients (0.8%) at the first consultation, and in 22 (4.4%) at the last. On echocardiographic study, alterations were seen in 267 patients (52.5%) at baseline, and in 273 patients (54.7%) at the end of the observation period. These included mild aortic valve abnormalities (mild regurgitation in two patients) and left atrial dilatation (four patients). Nevertheless, the overall improvement in these parameters should be noted. Concerning the 347 hypertensive patients (69.2%) who underwent ABPM, at the end 14 patients (2.9%) were found to have uncontrolled hypertension. The absence of acute episodes, such as MACE, during the study period should be noted.

Doppler ultrasound of the supra-aortic trunks showed an improvement in the number of patients with normal results from 82 patients (16.2%) to 100 (19.8%). IMT also improved, from an initial median of 2.90 mm to a final median of 1.40 mm (Wilcoxon signed-rank test, p<0.001). However, there was no reduction in the number of cases of vascular stenosis (McNemar test, p=0.500).

It should be noted that, of the 435 patients (85.4%) with hepatic steatosis, 208 (40.8%) presented hepatic steatosis with hepatomegaly (non-alcoholic fatty liver disease [NAFLD]).[11] Nevertheless, liver function was only altered in a small number of patients (14.5%).

The kidney is one of the target organs of CVD. Our assessment of renal function showed that overall, 46.7% (241/516) of patients had abnormal creatinine clearance (mean 104.13±46.18 ml/min/m^2, median 98.20; range 11.3-276.3), normal being defined as 70-135 ml/min/m^2. Moreover, creatinine levels were abnormal in 31.8% (164/516) of patients, with mean levels of 87±0.34 g/dl (median 0.81; range 0.39-4.5), normal being defined as 0.66-1.25 g/dl. Mean creatinine level was 0.87±0.34 g/dl (median 0.81; range 0.39-4.5). Finally, 31% (160/516) of patients were found to have abnormal urea levels, normal being defined as 10-50 mg/dl. Mean urea level was 47.09±17.41 mg/dl (median 41.00 mg/dl; range 17.0-259.0).

Nosological groups

Clinical diagnoses were classified into the following nosological groups: 390 patients with cardiovascular disease (75.6%), 50 with cerebrovascular disease (9.7%), 491 with metabolic diseases (95.2%) and 301 with behavioral diseases (58.3%).

Stratification of cardiovascular risk

Initial and final cardiovascular risk was stratified by estimating 10-year risk according to the parameters of the FRS, SCORE and ASCVD. Differences between cardiovascular risk scores calculated before and after treatment were as follows: FRS: -15.37 (min-max: -79.20-28.60), high-risk SCORE: -1.08 (min-max: -26.36-4.31), low-risk SCORE: -0.44 (min-max: -14.50-2.83) and ASCVD: -5.83 (min-max: -87.73-40.12). All improvements in cardiovascular risk scores between initial and final measures were statistically significant (p<0.05), regardless of the calculation method applied (Figure 1).

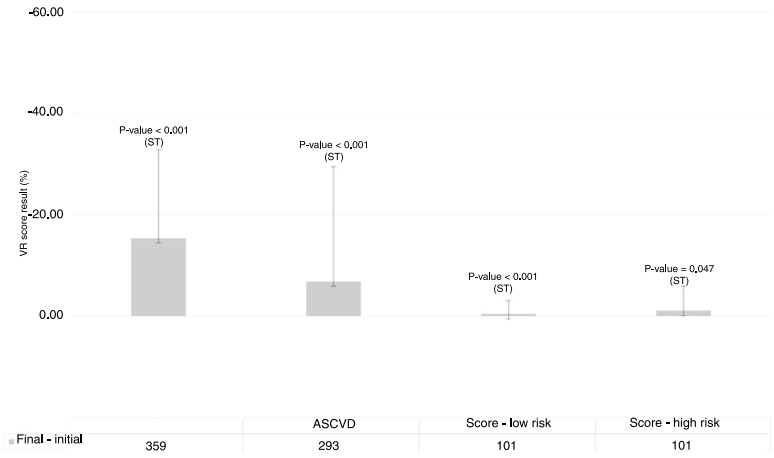

Figure 1 Differences between after treatment and before treatment for VR score calculated by each reference model. ASCVD: atherosclerotic cardiovascular disease; FRS: Framingham risk score; SCORE: systematic coronary risk evaluation.

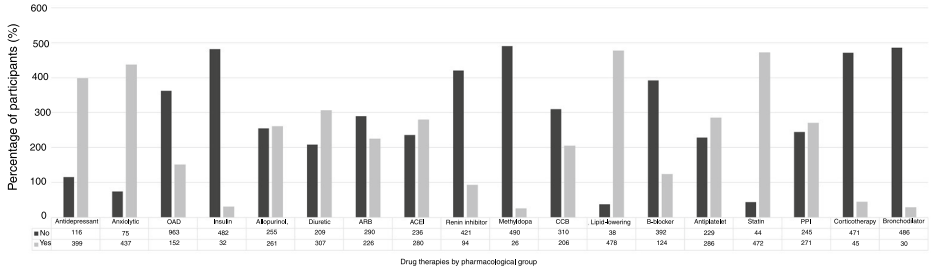

Figure 2 Drug therapies by pharmacological group and percentages of patients under treatment. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; OAD: oral antidiabetic drug; PPI: proton pump inhibitor.

Pharmacological therapy

The pharmacological therapies administered to the patients are presented in Figure 2 and Table 4, divided into pharmacological groups. The following therapies were used most in this patient group: antidepressants (particularly selective serotonin reuptake inhibitors [SSRIs]), anxiolytics, lipid-lowering therapy including statins, and antiplatelets. Allopurinol, diuretics, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were also commonly used. We also compared the efficacy of each of these therapies individually between patients who were receiving a particular treatment and those who were not, based on final Lp(a) levels. Results of the multiple regression analysis are shown in Supplementary Table 1. Briefly, statins, ACEIs, ARBs, oral antidiabetic drugs (OADs), antiplatelets, calcium channel blockers (CCBs) and allopurinol showed statistically significant differences on bivariate analysis ($p<0.05$) and were selected to enter the final model. This analysis excluded patients who died.

Overall, the use of statins, ACEIs, ARBs, OADs, antiplatelets, CCBs and allopurinol was associated with greater reductions in Lp(a) values during the follow-up period. The final optimized regression model showed that the regression coefficient for reduction in Lp(a) levels in patients under statins between the initial and the final measurement was more than 10.635, compared to those not under statins, after adjustment for antiplatelets, allopurinol and antidepressants (final model variables). Furthermore, the regression coefficient for reduction in Lp(a) levels in patients under antiplatelets was more than 4.786, compared with those not under antiplatelets, after adjustment for statins, allopurinol and antidepressants. The regression coefficient for reduction in Lp(a) levels in patients under allopurinol was more than 5.376, in comparison with those who were not under allopurinol, after adjustment for statins, antiplatelets and antidepressants. Finally, the regression coefficient for reduction in Lp(a) levels in patients under antidepressants was more than 4.367 compared with those who were not under antidepressants, after adjustment for statins, antiplatelets and allopurinol.

Discussion

In this retrospective observational study, we appraised the effects of using combined drug therapies on changes in Lp(a) levels in patients with high cardiovascular risk, without MACE. Overall, our results indicate significant clinical improvements between the initial and final measurements, especially regarding blood pressure and metabolic risk factors.

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Table 4 Associations between gender and pharmacological therapies and changes in Lp(a) levels between the initial and final measurement (excluding patients who died).

Variables	n	Mean difference	Median difference	Range (min-max)	p
Gender					
Female	279	-30.74±14.75	-29.00	-68.00-4.00	0.060 (MW)
Male	202	-33.50±16.17	-32.00	-71.00-4.10	
Statins					
No	38	-18.33±12.70	-18.00	-60.00-4.10	<0.001 (MW)
Yes	443	-33.06±15.07	-31.00	-71.00-4.00	
ACEIs					
No	222	-27.89±14.87	-25.00	-68.00-4.10	<0.001
Yes	259	-35.33±15.05	-34.00	-71.00-0.00	(MW)
ARBs					
No	274	-29.35±14.35	-27.00	-68.00-4.10	<0.001 (MW)
Yes	207	-35.27±16.12	-34.00	-71.00-0.00	
OADs					
No	337	-30.04±15.39	-27.00	-71.00-4.10	<0.001 (MW)
Yes	143	-36.20±14.62	-36.00	-71.00-8.00	
Antiplatelets					
No	217	-27.31± 14.84	-24.40	-70.00-4.10	<0.001 (MW)
Yes	263	-35.73± 14.84	-36.00	-71.00-0.00	
CCBs					
No	290	-29.00±14.74	-27.00	-70.00-4.10	<0.001 (MW)
Yes	191	-36.29±15.39	-35.00	-71.00-0.00	
Allopurinol					
No	242	-27.85±14.11	-25.00	-68.00-4.10	<0.001 (MW)
Yes	239	-35.99±15.61	-36.00	-71.00-0.00	
Antidepressants					
No	102	-30.23±14.59	-27.00	-71.00-4.10	0.303 (MW)
Yes	379	-32.34±15.60	-30.00	-71.00-4.00	

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCBs: calcium channel blockers; MW: non-parametric Mann-Whitney test; OAD: oral antidiabetic drugs; SD: standard deviation.

Neither social nor demographic factors appeared to pose difficulties in following the proposed treatments and guidance for improving lifestyles. The improvements in blood pressure control and significant reductions in waist circumference should be noted, as these are important cardiovascular risk factors influencing the atherosclerotic process.

This study demonstrated a significant correlation between Lp(a) levels and cardiovascular risk scores in patients with high cardiovascular risk but without MACE. In previous work, we found that increased Lp(a) levels in these individuals were strongly associated with cardiovascular risk factors such as IMT, LDL-C and homocysteine, as well as with NAFLD.[12] In addition, for the same population, a positive and significant correlation was found between Lp(a) and the risk scores used for CVD stratification ($p<0.001$).[12] These data suggest that guidelines for assessing the severity of the atherosclerotic process should be reviewed.[13]

Until recently, Lp(a) has been a recognized but underappreciated cardiovascular risk factor, largely because a therapeutic approach has yet to be established.[14,15] As specific treatments are lacking, Lp(a) warrants further investigation.[1] Early primary prevention is recommended, with the introduction of available therapies in clinically stable patients, regardless of vascular age risk (personal, family and lifestyle) and metabolic alterations promoting the atherosclerosis process. However, currently used cardiovascular risk scores do not fit this interventional approach, but rather delay the administration of combined drug treatments. Patients' commitment to implementing changes, including adopting healthier lifestyles,[16–18] such as regular exercise, is essential to the success of the treatment.[8,19]

Lp(a) acts as a marker of severity and progression of CVD in patients at particular risk for poor outcomes.[20] In our study, although there was a significant decrease in IMT, cases of carotid stenosis persisted after the treatment period.[20] Therefore, although this was not evident in previous studies, lipid-lowering therapy, especially statins combined with other treatments, appears to be involved in Lp(a) reduction. Similar results were obtained with ACEIs, diuretics, ARBs, CCBs and antiplatelets. The effects of allopurinol, OADs and proton pump inhibitors in combined drug therapy, should also be highlighted. On the other hand, beta-blockers and insulin had less effect.

These results confirm that the role of Lp(a) as a biomarker of cardiovascular risk should be analyzed along with that of patients' lifestyles and biochemical parameters. Lp(a) may thus be a crucial indicator for comprehensive early multidisciplinary treatment, directed at all cardiovascular risk factors and associated comorbidities.

A large proportion of patients had moderate renal failure, as expected since the kidney is a target organ for atherosclerotic disease, and also due to cellular senescence. This finding indicates that appropriate adjustments to therapy may be required. We also observed a high number of patients with hepatic steatosis, which indicates that this condition should be considered in the presence of NAFLD and, as such, may represent a way to contextualize the evolution and severity of atherosclerotic disease.[11,21]

In view of the clinically relevant and statistically significant reduction of Lp(a) seen in our study,[22] further research is required to establish a consistent therapeutic strategy to achieve this end,[23] as well as to improve upon the subjective calculation of cardiovascular risk with currently used algorithms. Nonetheless, we can state that first-line therapies should include statins,[24,25] allopurinol, antiplatelets and antidepressant drugs. In addition, the atherogenicity of Lp(a) may be modified through substantial reductions in LDL levels.

Although clinically relevant, our results should be interpreted in the light of the inherent methodological limitations of the study. As it is based on data from a single center, the results cannot be extrapolated to the Portuguese population in general. Due to its retrospective nature, the study could have been affected by information bias from data gathered from patients' charts, including changes in therapeutic guidelines over the long follow-up period (median 11.0 years). Furthermore, it was not possible to establish temporal relationships between risk factors and CVD that demonstrate causation.

Conclusion

Lp(a) is a key indicator of global cardiovascular risk and should be considered a therapeutic target. According to the results obtained for our patients, it may be important to initiate primary prevention, including combined drug therapies, while addressing all cardiovascular risk factors, to delay the atherosclerotic process. First-line therapy should include statins, antiplatelets, allopurinol and antidepressants, particularly SSRIs. Among other pharmacological therapies, CCBs, ACEIs, OADs and ARBs should also be considered, as well as lifestyle modifications.

Conflicts of interest

The author has no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2019.01.006.

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DISCUSSÃO

Este estudo permite constatar que os valores médios de Lp(a) estão substancialmente aumentados nos doentes de elevado risco cardiovascular e, mais que isso, estão diretamente correlacionados com outros FRCV.

Pela primeira vez ficou demonstrada a existência de uma correlação estatisticamente significativa, entre os valores elevados de Lp(a) com os valores obtidos no cálculo do risco cardiovascular a 10 anos através das tabelas de algoritmos mais em uso: FRS, ASCVD, SCORE, incluindo também o de baixo risco cardiovascular aplicável à população Portuguesa.

Observou-se uma correlação significativa ($p<0.001$) entre Lp(a) com a IMT, IMC, LDLc, Homocisteína, PCR, perímetro abdominal, sendo de realçar que a mesma não se encontrou relativamente ao HDLc.

O efeito pró inflamatório da Lp(a) é corroborado na sua correlação com a PCR.

De assinalar a significativa correlação entre Lp(a) e esteatose hepática, sendo que os valores de Lp(a) aparecem aumentados na esteatose hepática. Esta situação exige estudos ulteriores no sentido de se determinar se e qual a relação no contexto de doença hepática não alcoólica (NAFLD) sem outras causas secundárias para a esteatose.

O fígado é o "*hub*" central do metabolismo das lipoproteínas regulando o balanço entre a beta-oxidação e a síntese de lípidos, como também a produção da maioria das apolipoproteínas. Estudos prospetivos têm associado a NAFLD com a DCV, sendo que ainda não foi possível provar tal relação face à heterogeneidade dos métodos e de critérios diagnósticos utilizados, daí que não seja correto considerar a presença de NAFLD na estratificação do risco como nas decisões terapêuticas para a DCV.

Apesar dos resultados obtidos indicarem que existe um aumento nos valores de Lp(a) de acordo com o grupo etário, a correlação positiva entre a Lp(a) e os scores de risco vascular indicam que a Lp(a) constitui um fator decisivo na perceção precoce e consequente avaliação do risco vascular. Esta informação será da maior relevância porquanto permite um adequado e atempado planeamento, reavaliação da intervenção e determinar orientações terapêuticas adequadas em prevenção primária.

A acumulação de partículas de Lp(a) nas lesões ateroscleróticas ocorre com mais facilidade devida à sua maior afinidade pela parede arterial que as LDLc. A Lp(a) condiciona alterações metabólicas, entre outras o aumento da proliferação e migração de células musculares lisas, determina a expressão molecular da adesão endotelial e, a formação de "*foam cells*" induzindo o processo aterosclerótico.

A Lp(a) e LDLc estão independentemente associados ao risco de DCV, sendo consensual que níveis adequados e controlados de LDLc (<70 mg/dl) em prevenção primária conduzem a uma atenuação do risco provocado pela Lp(a), apesar da sua persistência em valores elevados. Assim e porque o perfil lipídico é passível de condicionar a intensidade do risco devido aos valores elevados de Lp(a) e, porque a redução

dos níveis de LDLc atenuam o efeito deletério da Lp(a) no processo aterosclerótico e na DCV, também devem ser consideradas as alterações nos estilos de vida tendo em conta, entre outros, os benefícios da dieta, da actividade física regular e, controlo adequado de todos os demais FRCV modificáveis. Sendo que ainda não existe qualquer demonstração do impacto direto destas medidas nos níveis de Lp(a).

Considerando estes resultados na população Portuguesa aceita-se que a dieta mediterrânica será uma parte essencial na prevenção primária, mas não deverá ser sobre avaliada em detrimento dos demais FRCV associados a DCV, sob pena de serem adiadas intervenções precoces que podem ser decisivas para a redução da patologia cardiovascular.

Porque a Lp(a) esta associada aos FRCV convencionais incluindo os elevados níveis de LDLc, está aumentada nos doentes com esteatose hepática e naqueles de elevado risco vascular, são factos que se conjugam para que se considere como um biomarcador de referência, determinante para uma intervenção precoce e diversificada, com orientações e terapêuticas intensivas no contexto da prevenção primária da DCV.

A Lp(a) é conhecida desde 1961 e foi depreciada ao longo dos tempos. Por um lado face ao entusiasmo pela evolução de excelência dos resultados obtidos para a redução da morbilidade e mortalidade por DCV e, por outro lado, face às manifestas dificuldades na sua abordagem terapêutica específica, que ainda persiste. Aqui chegados, constatamos a existência de um risco cardiovascular residual difícil de ultrapassar, que condiciona uma retração naquela sequência exponencial de excelentes resultados que veem sendo conseguidos, em particular nas três últimas décadas relativamente à mortalidade e morbilidade por DCV.

A evolução na patologia molecular associada a novos conhecimentos sobre as implicações genéticas inerentes à DCV, fazem renascer o interesse pelo metabolismo das lipoproteínas. Entretanto iniciado nos anos setenta do século passado com o despertar da hepatologia na *Sheila Sherlock´s Liver Unit of Royal Free Hospital in London*. Iniciou-se o isolamento das lipoproteínas e quantificação dos lípidos, abrindo caminho para conhecimentos importantes que permanecem atuais. Na década passada, os inexoráveis avanços na genética e na patologia molecular trouxeram novos conhecimentos e desafios relativos ao metabolismo das apoliproteínas e das lipoproteínas entre estas a Lp(a).

Desde há décadas que se conhece a relação estreita entre a Lp(a) com o risco vascular.

O nosso trabalho permitiu pela primeira vez determinar a existência de uma correlação estatisticamente significativa entre Lp(a) e risco cardiovascular a 10 anos calculado por via dos algoritmos mais usados.

A facilidade da sua determinação, o seu baixo custo, a sua potencial e decisiva importância para um diagnóstico precoce e independente da idade do doente, torna a Lp(a) fundamental para a definição, conceptualização de estratégias e de orientações terapêuticas no contexto da prevenção primária. A prossecução destes objetivos, também implica a cumplicidade do doente na adesão à terapêutica e na implementação de estilos de vida saudáveis: seja na redução do consumo de álcool, de sal e de açúcar, como enfrentar o tabagismo, enveredar pela prática regular de exercício físico aeróbico e, tudo fazer no sentido de poder usufruir de repouso saudável.

No nosso trabalho foi notória a cumplicidade dos doentes na significativa melhoria dos FRCV modificáveis, evidenciados na redução do consumo de álcool, no consumo de tabaco e nos excelentes níveis de adesão à prática regular de exercício físico aeróbio, para além da adesão às terapêuticas propostas.

Os resultados apresentam uma evolução positiva e estatisticamente significativa relativamente a vários parâmetros fundamentais na avaliação do risco cardiovascular. Relativamente à evolução antropométrica verificam-se reduções significativas ($p < 0.001$) na circunferência abdominal, na PCT e PB.

Deve-se realçar o adequado controlo da pressão arterial. Assim como, a importante e estatisticamente significativa redução do IMT sendo que os casos de estenose carotídea persistiram.

Relativamente à evolução dos resultados nos parâmetros bioquímicos, constatamos um evolução estatisticamente significativa ($p<0.001$) no decréscimo dos níveis de PCR, HgA1c, Frutosamina, Colesterol total, LDLc, VLDLc, Triglicerideos, Fibrinogénio, Homocisteína, Lp(a), Ácido úrico e na microalbuminuria, com significativo aumento dos níveis de HDLc.

Neste contexto, também nos propusemos avaliar as consequências dos tratamentos efetuados, considerando desde logo e para o efeito a associação entre sexo, tempo de observação e tratamentos baseados na variação de Lp(a) entre o início e a conclusão do estudo. Na análises de regressão múltipla com modelo para a Lp(a) entre o início e final do tratamento verificamos a significativa importância das estatinas, antiagregantes plaquetários, alopurinol e os antidepressivos (Inibidores da recaptação da serotonina) para um valor $p<0.001$.

Os nossos resultados permitem-nos afirmar, um pouco a exemplo do que sucedeu com o estudo "Júpiter" e depois de certa forma com os "*Insights from Saturn*", que terapêutica de primeira linha e em prevenção primária para a redução da Lp(a) são as estatinas em dosagem intermédia e de forma perene. Resultados idênticos relativamente aos IECA, Diuréticos, ARA-II, ACC, e antiagregantes plaquetários. A associação de alopurinol, ADO, e inibidores da bomba de protões devem ser realçados pelos resultados obtidos, sendo que o efeito dos betabloqueadores e da insulina ficaram aquém do que seria expectável.

A relação estatisticamente significativa entre a Lp(a) e os scores do risco vascular obtidos pelas cartas de cálculo de risco vascular por via dos algoritmos, poderá constituir um contributo no sentido de uma futura revisão das *guidelines*, para que passe a haver uma abordagem ao risco vascular de forma precoce, diferente e independente da idade, face a severidade do processo aterosclerótico.

Fica patente um alerta da maior importância relativamente à Lp(a), que deverá ser continuamente investigada e estudada, mas nunca subestimada. Considerando a importância decisiva da Lp(a) na implementação e desenvolvimento do processo aterosclerótico e suas consequências, apesar de ainda não dispormos de terapêutica específica para a sua abordagem.

Sendo a Lp(a) o marcador de referência para os doentes de elevado risco cardiovascular, é natural que seja constituída alvo terapêutico a exemplo do que vem sucedendo nos múltiplos estudos recentemente publicados.

A intervenção primária muito precoce é a matriz recomendada, com a introdução de terapêuticas específicas mesmo nos doentes com a situação clínica estável, atentando-se ao risco vascular considerando o estilo de vida, antecedentes pessoais e familiares, a idade vascular assim como a presença de alterações metabólicas promotoras do processo aterosclerótico.

A avaliação do risco vascular por via dos algoritmos não se coaduna com esta matriz de intervenção e poderá promover atrasos na introdução de orientações e de terapêuticas combinadas.

A cumplicidade do doente é fundamental na adequação a estilos de vida saudáveis, sendo de relevar que no nosso estudo, os fatores sociais e demográficos não constituíram qualquer dificuldade que obstasse a que os doentes cumprissem os tratamentos e orientações propostas, nomeadamente na adequação do estilo de vida.

A terapêutica antidislipidemica e em particular as estatinas de intensidade intermedia de longa duração, desempenharam um papel decisivo na obtenção destes resultados e na redução dos níveis da Lp(a). Resultados significativos também foram conseguidos com os IECA, diuréticos, ARA-II, ACC e antiagregantes plaquetários. Destaque para a significativa importância do alopurinol, ADO e dos IBP no contexto da terapêutica combinada. De registar os resultados menos bons atribuídos aos beta bloqueantes e à insulina.

Estes resultados confirmam a importância da Lp(a) como biomarcador do risco cardiovascular, crucial na decisão para uma intervenção precoce e multidisciplinar, que deverá ter como objetivo o tratamento global e dirigido a todos os FRCV associados a demais alterações metabólicas.

Uma referência para o elevado número de doentes com insuficiência renal moderada, que poderá estar relacionada com o facto de o rim ser um dos órgãos alvo do processo aterosclerótico, de várias patologias metabólicas associadas, como poder ter relação com a senescência celular. Contudo, deve realçar-se que também poderá ser o resultado de ajustamentos terapêuticos que poderão não ter sido atualizados, devendo recordar-se que a mediana do nosso estudo é de 12 anos, um longo período com atualizações e inovações diagnósticas e terapêuticas propostas em sucessivas *guidelines*.

Relativamente ao elevado número de doentes com esteatose hepática sem alteração na função hepática, a mesma é considerada no contexto da NAFLD e, poderá constituir uma "janela" para avaliação clinica da evolução e contextualização da doença aterosclerótica.

Face à significativa redução dos níveis de Lp(a), será necessário dar continuidade a este trabalho com estudos ulteriores, entre outros no sentido de se estabelecer uma estratégia de abordagem diagnóstica e terapêuticas consistentes, que também poderão passar pela revisão do cálculo do risco cardiovascular.

CONCLUSÕES

A Lp(a) é um forte indicador de risco cardiovascular diretamente correlacionado com os demais marcadores e com a esteatose hepática não alcoólica.
Considerando as evidencias clinicas e epidemiológicas, a facilidade na sua determinação, assim como o seu baixo custo deverá fazer parte da avaliação de rotina do risco cardiovascular particularmente na prevenção primária.

Lp(a) é um indicador de risco vascular global, que deve ser abordado numa perspetiva global e, como tal deve ser considerada um alvo terapêutico.
Iniciar precocemente a prevenção primária com inclusão de todas as terapêuticas combinadas dirigidas aos vários FRCV no sentido de atenuar o processo aterosclerótico.

As estatinas constituem a terapêutica de primeira linha, devendo também ser considerados os antiagregantes plaquetários, alopurinol e o tratamento antidepressivo. Sempre que a situação clinica o permita os ACC, IECA, ADO, e ARA-II bem como adequação a estilos de vida saudáveis.

LIMITAÇÕES

Esta investigação tem algumas limitações inerentes ao seu desenho e natureza observacional. A interpretação dos nossos resultados deve levar em consideração possíveis fatores de variação e controlo individuais como seja o IMC, pressão arterial e parâmetros laboratoriais como a PCR ou HgA1c, bem como os indivíduos omitidos (dados ausentes), durante o período do estudo. Apesar destas limitações, este estudo faculta-nos dados únicos sobre o perfil de Lp(a) em pacientes portugueses com elevado risco de doenças cardiovasculares, determinando implicações na prática clinica e em particular, na prevenção primária!

A Lp(a) é de facto uma ferramenta fundamental na perceção, avaliação e prevenção do risco cardiovascular, particularmente na prevenção primária. A sua correlação com os novos meios diagnósticos e métodos de imagem poderá constituir o ponto de viragem na sua abordagem com consequente diminuição do Risco Vascular residual.

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